

Prognosticating Retinal Dystrophies in the Postgenomic Era

Inheritance patterns of retinal diseases.

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Inherited retinal dystrophies are a genetically heterogeneous group of disorders. They can be classified in various ways including by clinical findings, electrophysiologic findings, or by inheritance patterns. One of the most important early steps in the clinical evaluation of retinal dystrophy patients is to obtain a family history. If possible, family members can be examined as well to form the inheritance pattern. This article discusses retinal dystrophies as grouped by inheritance patterns, and Table 1 lists causative genes. If there are no other family members affected, the disease is likely to have an autosomal recessive inheritance pattern. Rarely, a sporadic case could also mean a new autosomal dominant mutation has developed. The hallmarks of established autosomal dominant diseases are that every generation is affected and that a male-to-male transmission occurs. On the other hand, X-linked recessive disorders almost exclusively occur in male patients and are transmitted maternally. The most uncommon inheritance pattern is X-linked dominance. These patients are almost always female, as X-linked dominant traits are generally lethal in males. A careful family history is essential for diagnosis and genetic counseling.

AUTOSOMAL RECESSIVE INHERITANCE

Generalized progressive. Retinitis pigmentosa (RP) is the most common form of inherited retinal degeneration, affecting one in 3,000 people.^{1,2} It is a heterogeneous group of diseases characterized by progressive rod-cone dysfunction (Figure 1). Patients initially present with nyctalopia from rod photoreceptor loss, progress to tunnel vision, and ultimately central vision

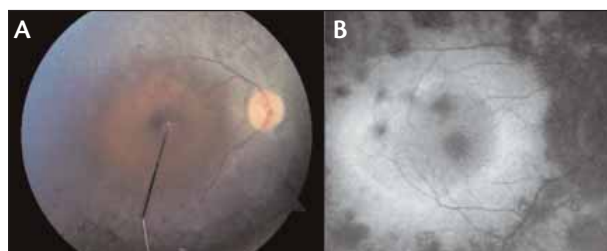


Figure 1. Thirty-five year old man with autosomal recessive RP. Color fundus photograph showing intraretinal pigment migration, RPE atrophy, and attenuated arterioles. Note fixation stick (A). Autofluorescence demonstrating a hyperfluorescent ring in the macula and large patches of hypofluorescence around the arcades due to atrophic RPE (B).

is affected. Electro-retinogram (ERG) provides a generalized assessment of rod and cone function. In RP patients, electrophysiological disturbances precede photoreceptor loss, and ERGs are abnormal even before changes can be seen on fundus examination.^{1,3} The autosomal recessive form of RP is its most common form.⁴

Leber congenital amaurosis (LCA) is a severe subtype of rod-cone dystrophy, which most commonly has autosomal recessive inheritance.^{5,6} The autosomal dominant form is caused by mutations in CRX.⁷ Depending on the gene involved, fundus examination can vary. Patients can have early onset of decreased vision with nystagmus and frequently normal fundus appearance. A mutation in the RPE65 gene causes one particular form of autosomal recessive LCA known as LCA2.

The first trials to test gene therapy's efficacy in restoring vision were done in 2001 when Jean Bennett

TABLE 1. THE FOLLOWING GENE NAMES ARE USED IN THE ONLINE MENDELIAN INHERITANCE IN MAN (OMIM) DATA BASE. ([HTTP://WWW.NCBI.NLM.NIH.GOV/SITES/ENTREZ?DB=OMIM](http://www.ncbi.nlm.nih.gov/sites/entrez?DB=OMIM))

Inheritance Pattern	Clinical sub-type	Disease	Known Genes
Autosomal recessive	Generalized progressive	Retinitis pigmentosa	CERKL, CNGA1, CNGB1, MERTK, PDE6A, PDE6B, PNR, RDH12, RGR, RLBP1, SAG, TULP1, CRB, RPE65, USH2A, USH3A, LRAT
		Cone-rod dystrophy	ABCA4, CACNA2D4, CNGB3, KCNV2, RAX2, RDH5
		Leber	AIPL1, CRB1, CRX, GUCY2D, LRAT, TULP1, MERTK, CEP290, RDH12, RPGRIP1, LCA5 RPE65
		Bardet-Biedl syndrome	ARL6, BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BBS10, BBS12, MKKS, TRIM32, TTC8
		Usher	CDH23, CLRN1, DFNB31, GPR98, MYO7A, PCDH15, USH1C, USH1G, USH2A
		Syndromic/systemic diseases	ABCC6, AHI1, ALMS1, CC2D2A, CEP290, CLN3, COL9A1, INVS, IQCB1, LRP5, MTP, NPHP1, NPHP3, NPHP4, OPA3, PANK2, PEX1, PEX7, PHYH, PXMP3, RPGRIP1L, TTPA, WFS1
	Generalized stationary	Achromatopsia	CNGA3, CNGB3, GNAT2
		Rod system: CSNB	CABP4, GRK1, GRM6, RDH5, SAG
	Macular	Stargardt	ABCA4
		Bull's eye	
Autosomal dominant	Generalized progressive	Retinitis pigmentosa	CA4, FSCN2, IMPDH1, NRL, PRPF3, PRPF31, PRPF8, RDS, RHO, ROM1, RP1, RP9, CRX, SEMA4A, TOPORS
	Generalized stationary	CSNB	GNAT1, PDE6B, RHO
	Macular	Bull's eye	MCDR2
		Best	VMD2
		Pattern dystrophies	RDS/PRPH2
		North Carolina	MCDR1
		Doyne honeycomb/malattia Leventinese	EFEMP1
		Sorsby	TIMP3
		Stargardt-like dominant maculopathy	ELOVL4
X-linked recessive	Generalized progressive	Retinitis pigmentosa	RPGR, RP2
		Choroideremia	CHM
		Juvenile retinoschisis	RS1
	Generalized stationary	CSNB	NYX, CACNA1F
X-linked dominant	Generalized stationary	Aicardi syndrome	Unknown
		Incontinentia pigmentosa	NEMO

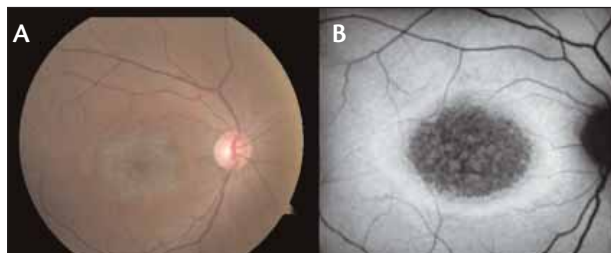


Figure 2. Thirty-year-old man with bull's eye maculopathy of unknown mutation. Color fundus photograph demonstrating atrophic RPE in an annular configuration (A). Autofluorescence shows hyperfluorescent ring surrounding an area of mottled, devitalized RPE (B).

at the University of Pennsylvania, Greg Acland at Cornell University, Bill Hauswirth at the University of Florida and colleagues restored retinal function in Briard dogs affected with LCA2.⁸ The eye is an ideal target for gene therapy because it is a relatively immune-privileged site, intraocular injection minimizes systemic side effects and results can be noninvasively measured with studies such as fundus photography, autofluorescence and ERGs.⁹ In two recent studies of six young adult human patients with LCA2, the introduction of RPE65 via an adeno-associated virus by subretinal injection proved safe, and four patients reported improvement (See "Leber's Congenital Amaurosis: Safety, Efficacy in Early Clinical Investigation," page 50).^{10,11}

Cone disorders are a family of diseases characterized by cone dysfunction. They can be stationary or progressive; its associated symptoms include color vision loss and hemeralopia. Because cone disorders affect central vision early, they tend to manifest more severely than RP. Frequently, progressive cone dystrophy turns into cone-rod dystrophy later in life. Patients with progressive cone disorders have a poor prognosis and should familiarize themselves with visual aids. In stark contrast, patients with stationary disorders such as achromatopsia or congenital stationary night blindness are able to read and have a relatively good prognosis with virtually no limitations to their careers.

Bull's eye maculopathy (BEM) is a descriptive term for a dark central region around the fovea and a paler surrounding ring (Figure 2). BEM can appear in cone dystrophy, cone-rod dystrophy, rod-cone dystrophy, or medication toxicities such as hydroxychloroquine sulfate toxicity.¹² Most commonly, the cause of BEM is unknown but ABCA4 defect is the most common known cause of BEM.¹³

Generalized nonprogressive. Achromatopsia is a rare form of stationary cone dysfunction presenting in infancy with nystagmus. There are complete (typical)

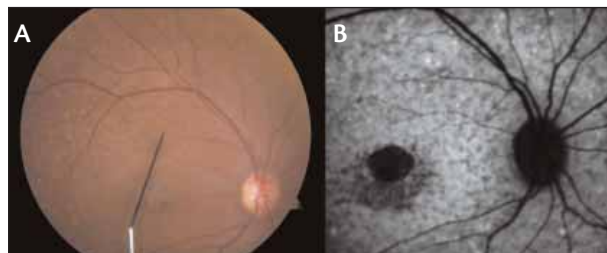


Figure 3. Twenty-five-year-old woman with Stargardt disease. Color fundus photograph illustrates pisciform yellow flecks. Note RPE atrophy of the fovea and fixation stick (A). Autofluorescence shows hyperfluorescent flecks due to lipofuscin accumulation and hypofluorescent areas of atrophic RPE (B).

and incomplete (atypical) types of achromatopsia. Patients with incomplete achromatopsia have better visual acuity and retain some color vision. Currently, three genes have been implicated in achromatopsia: CNGA3, CNGB3, and GNAT2.⁹ The transducin subunit in cones, GNAT2 (OMIM+139340) has been linked to both types of achromatopsia.¹⁴

Macular. Macular dystrophies affect the posterior pole, resulting in impaired central vision but unaffected peripheral vision. Because peripheral vision is unaffected, patients with macular dystrophies have a better prognosis than progressive cone dystrophy patients. Patients with macular dystrophies tend to have normal full-field ERGs, but retinal pigment epithelium and photoreceptors undergo degeneration. Stargardt disease, the most common inherited macular disease, is autosomal recessive and characterized by lipofuscin accumulation in the RPE.⁶ Patients with Stargardt disease can have stereotypical yellow "fish-tail" flecks at the level of the RPE (Figure 3) and progress to macular atrophy (Figure 3). ABCA4, the gene implicated in all forms of Stargardt disease, encodes for a protein called Rim.¹⁵ Located in the rims of photoreceptor disc membranes, this protein is involved in transporting a vitamin A intermediate to the RPE and preventing lipofuscin accumulation. Relative to the other dominant forms of macular dystrophies, the prognosis of patients with Stargardt disease is relatively poor.

AUTOSOMAL DOMINANTLY INHERITED

Generalized. About 15% to 35% of all cases of RP are autosomal dominantly inherited.^{16,17} These RP patients tend to have a milder disease with a slower course than autosomal recessively inherited RP and present later in life. Thirty percent of autosomal dominant forms of RP involve a gain of function mutation in rhodopsin.¹⁸

The autosomal dominant form of cone dysfunction is rare and has a poor prognosis. Patients present with reduced visual acuity and loss of color vision in early adulthood and progress to legal blindness. Autosomal dominantly inherited cone dysfunction has been associated with guanylate cyclase-activating protein 1 (GCAP1), which is involved in forming cGMP in the phototransduction cascade.¹⁹

Macular. Similar to RP, macular dystrophies with autosomal dominant inheritance are less severe than the autosomal recessive macular dystrophy, Stargardt disease. For example, Best disease and peripherin/RDS pattern dystrophy are forms of macular dystrophies that are autosomal dominantly inherited and have a good prognosis.

Patients with RDS pattern dystrophy maintain relatively good visual acuity. They start losing one line of vision every 10 years from around age 40 and settle to a visual acuity of about 20/60 to 20/70. Best disease, also known as vitelliform macular dystrophy, is characterized by the appearance of an “egg yolk” lesion in the macula, resulting from lipofuscin accumulation in degenerating RPE cells (Figure 4).⁶ Choroidal neovascularization (CNV) is a complication that rarely develops with Best disease. As a corollary, children with unknown causes of CNV should be evaluated for Best disease.

Best disease can be asymptomatic and is diagnosed by a reduced Arden ratio on electrooculogram (EOG). Children unable to cooperate with electrophysiological testing can have their parents’ EOG taken because the disease has autosomal dominant inheritance. Best disease is caused by a mutation in the VMD2 gene encoding a protein called bestrophin that acts as a chloride channel on the basolateral membrane of the RPE.^{20,21} When Best disease presents in adulthood, its differential diagnosis includes adult vitelliform macular degeneration, a mild condition with age of onset occurring after 40 years. The inheritance pattern of adult vitelliform macular degeneration is autosomal dominant, but no gene is currently associated with the disease.

North Carolina macular dystrophy (NCMD) (OMIM#136550) is a rare condition of macular degeneration with congenital or infantile onset.¹⁴ Central vision is impaired and generally stable unless choroidal neovascularization develops. Visual acuity can range from 20/20 to 20/800. Fundus examination is highly variable: there may be a few drusen-like lesions, disciform scars, or macular colobomas. The MCDR1 gene has been linked to NCMD.²²

Doyme honeycomb dystrophy (DHCD) and malattia leventinese (OMIM#126600) are rare conditions that are identical to each other and characterized by drusen in

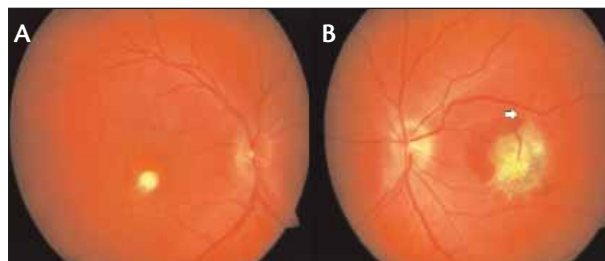


Figure 4. Nine-year-old boy with Best disease. Color fundus photograph of right eye with small vitelliform lesion in macula (A). Color fundus photograph of left eye with subretinal scar from choroidal neovascular membrane (B). Note possible retinal-choroidal anastomosis (white arrow).

the posterior pole of the eye, including the macula and the nasal side of the optic disc, occurring in early adult life.¹⁴ The drusen accumulations in DHCD form a honeycomb pattern, whereas the drusen in malattia leventinese radiate from the macula to the peripheral retina. In both conditions, there is slow loss of visual acuity unless complicated by choroidal neovascularization. Mutations in EFEMP1 have been implicated in both conditions.^{23,24}

X-LINKED RECESSIVELY INHERITED

Generalized progressive. The X-linked form of RP is the most severe form of RP. It has an early onset, with teenage males showing rod degeneration followed soon by cone degeneration. Female carriers can show patchy areas of rod degeneration presumably due to lyonization.²⁵ ERG in heterozygous carriers is affected by age 60. The retinitis pigmentosa GTPase regulator (RPGR) gene is now believed to be a major cause of X-linked RP.²⁶

Choroideremia (OMIM#303100) leads to degeneration of the choriocapillaris, RPE, and photoreceptors and has a distinct fundus appearance.¹⁴ Female carriers are not affected until age 60; males, however, maintain good central vision until after age 50.

X-linked retinoschisis (XLRS) (OMIM+312700) is a degeneration of the retina that leads to splitting of the inner nuclear layer (Figure 5).¹⁴ Poor visual function generally manifests around middle age, although affected babies may present with bilateral bullous detachments that often settle on their own. XLRS is diagnosed by an electronegative ERG, and patients generally lose one line of vision every 10 years. Mutations in the RS1 gene cause XLRS.²⁷

Generalized stationary. Congenital stationary night blindness (CSNB) is a group of inherited stationary retinal dystrophies characterized by a loss of rod function at birth but no progressive rod photoreceptor cell death. X-linked recessive is the most common inheritance pattern of CSNB, although autosomal dominant and autosomal

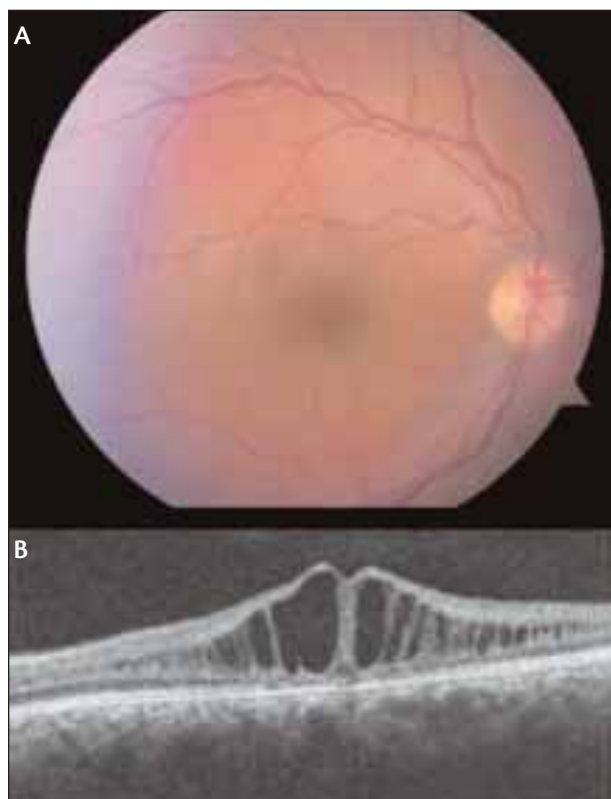


Figure 5. Thirty-five year old man with XLRS. (A) Color fundus photograph showing typical spokewheel appearance of schisis cavities. (B) Spectral high-resolution optical coherence tomography (OCT) with splitting of the inner nuclear layer.

mal recessive forms occur. X-linked CSNB is broadly categorized into complete CSNB and incomplete CSNB groups; it is believed that complete CSNB is caused by mutations in the NYX gene while incomplete CSNB is caused by mutations in the calcium channel gene, CACNA1F. Patients with X-linked CSNB typically have nystagmus and high myopia.

X-LINKED DOMINANTLY INHERITED

Aicardi syndrome (OMIM 304050) is a rare condition showing lacunae in the retina.¹⁴ Incontinentia pigmentosa is another rare condition characterized by a mottled diffuse hypopigmentation and abnormal peripheral blood vessels with areas of nonperfusion. Patients present with a variety of dermatologic findings.

SUMMARY

After many years of limited treatment options for inherited retinal dystrophies, gene therapy is becoming more of a possibility. The success of gene therapy is contingent upon understanding causative mutations and

molecularly diagnosing patients. This is, in part, being promoted with the use of commercially available gene chips to molecularly diagnose patients with inherited eye diseases.²⁸ Currently, Asper Ophthalmics (Tartu, Estonia) offers tests for several inherited retinal dystrophies using a microarray. An important first step in molecularly diagnosing patients is to establish the inheritance pattern of disease.²⁹ The microarray technology is mainly limited by the number of known mutations and the inclusion of a few benign polymorphisms. Genotyping and phenotyping studies of inherited retinal dystrophies will continue to be exciting for ophthalmologists and patients. ■

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This article is dedicated to the memory of Professor Victor A. McKusick, who repeatedly demonstrated that clinical observation can aid molecular understanding of disease mechanisms.

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